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(54) Title: ORAL PHARMACEUTICAL COMBINATIONS OF ANTIHISTAMINIC COMPOUNDS AND TERPENOIDS

(57) Abstract

Pharmaceutical compositions for oral administration comprising an antihistaminic compound and a terpenoid compound are disclosed. They are useful in the prevention or treatment of inter alia allergic rhinitis (hay fever), mild asthma and urticaria. Furthermore, the invention concerns a method of treating inter alia allergic rhinitis, mild asthma and urticaria which method comprises orally administering to a mammal including man a therapeutically effective amount of an antihistaminic compound together with a therapeutically effective amount of a terpenoid compound. Further the invention relates to the use of an antihistaminic compound together with a terpenoid compound (for the manufacture of a pharmaceutical composition adapted to oral administration) for the prevention or treatment of inter alia allergic rhinitis, mild asthma and urticaria.

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ORAL PHARMACEUTICAL COMBINATIONS OF ANTIHISTAMINIC COMPOUNDS AND TERPENOIDS

The invention relates to the oral prevention and treatment of rhinitis, sinusitis, asthma, atopic dermatitis, urticaria, pruritus and other inflammatory skin diseases with antihistaminic compounds as well as to novel pharmaceutical compositions adapted to oral administration comprising antihistaminic compounds.

The oral administration of antihistaminic compounds, especially H1 antagonists, for the prevention and relief of symptoms due to rhinitis, especially seasonal allergic rhinitis, is known in the art. Moreover, acute urticaria and atopic dermatitis, particularly the pruritic component thereof, are known to be alleviated by oral H1 antagonists.

It has now surprisingly been found that by combining an antihistaminic compound with a terpenoid compound in a pharmaceutical composition for oral administration the clinical efficacy of the combination is enhanced in an unexpected manner. Moreover, the combinations of the invention show, unexpectedly, a very much improved side effect profile, i.e. the adverse effects typical for orally administered antihistaminic compounds, such as dizziness or fatigue, nausea, constipation or diarrhea, or cardiac arrhythmia, can only be detected to a far lesser extent than with antihistamine monotherapy alone.

Therefore, the invention relates to the use of an antihistaminic compound in combination with a terpenoid compound (for the manufacture of a pharmaceutical composition adapted to oral administration) for the prevention or treatment of rhinitis, especially infectious rhinitis, allergic rhinitis (hay fever) or vasomotor rhinitis, sinusitis; asthma, especially mild asthma; atopic dermatitis, urticaria, pruritus and other inflammatory skin conditions, such as insect bites, sunburn or others burns.

An antihistaminic compound is especially a H1 receptor antagonist and is, for example, (a) an alkylamine derivative, e.g. acrivastine, bamipine, brompheniramine, chlorpheniramine, dexchlorpheniramine (= d-form of chlorpheniramine), dimethindene, Metron S, pheniramine, pyrrobutamine, thenaldine, tolpropamine or triprolidine; (b) an aminoalkyl ether, e.g. bietanautine, bromodiphenhydramine, carbinoxamine, clemastine, diphenylpyraline, doxylamine, embramine, medrylamine, mephenhydramine, p-methyldiphenhydramine, orphenadrine, phenyltoloxamine, piprinhydrinate or setastine; (c) an ethylenediamine

derivative, e.g. alloclamide, p-bromtripelennamine, chloropyramine, chlorothen, histapyrrodine, methafurylene, methaphenilene, methapyrilene, phenbenzamine, pyrilamine, talastine, thenyldiamine, thonzylamine hydrochloride, tripelennamine or zolamine; (d) a piperazine, e.g. cetirizine, chlorcyclizine, cinnarizine, clocinizine or hydroxyzine; (e) a phenothiazine tricyclic, e.g. ahistan, etymemazine, fenethazine, N-hydroxyethylpromethazine chloride, isopromethazine, mequitazine, methdilazine, promethazine, pyrathiazine, thiazinamium methylsulfate or trimeprazine; (f) a tricyclic other than phenothiazines, e.g. azatadine, clobenzepam, cyproheptadine, deptropine, isothipendyl, loratadine or prothipendyl; and (g) an antihistaminic compound of another structure, e.g. antazoline, astemizole, azelastine, cetoxime, clemizole, clobenztropine, diphenazoline, diphenhydramine, ebastine, emedastine, levocabastine, mebhydroline, phenindamine, terfenadine or tritoqualine.

The term "antihistaminic compound" is to be understood as also to include (1) any pharmaceutically acceptable salt of a free compound (acid or base) mentioned above, (2) any free compound (acid or base) or any other pharmaceutically acceptable salt of a salt mentioned above, and (3) any active metabolite of a compound mentioned above. Examples for active metabolites are carebastine, which is the active metabolite of ebastine; norastemizole, which is the active metabolite of astemizole, or terfenadine carboxilate, which is the active metabolite of terfenadine.

A pharmaceutically acceptable salt of an antihistaminic compound having a basic group is e.g. an acid addition salt. Suitable acid components may be, for example, strong inorganic acids, typically mineral acids, e.g. sulfuric acid, phosphoric acids, e.g. orthophosphoric acid, hydrohalic acids, e.g. hydrochloric acid, or strong organic carboxylic acids, typically lower alkanecarboxylic acids which may be substituted, e.g. by halogen, such as acetic acid or trifluoroacetic acid, dicarboxylic acids which may be unsaturated, e.g. oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, hydroxycarboxylic acids, e.g. ascorbic, glycolic, lactic, malic, tartaric or citric acid, amino acids, e.g. aspartic or glutaminic acid, or benzoic acid, or organic sulfonic acids, typically lower alkanesulfonic acids which may be substituted, e.g. by halogen, typically methanesulfonic acid, or arylsulfonic acids which may be substituted, e.g. by lower alkyl, typically p-toluenesulfonic acid.

A pharmaceutically acceptable salt of an antihistaminic compound having an acidic group is e.g. an alkali metal or alkaline earth metal salt, e.g. the sodium, potassium, magnesium or calcium salt, an aluminium salt or a transition metal salt, e.g. the zinc or copper salt, or a corresponding salt with ammonia or organic amines. Organic amines that come into consideration are, for example, the following: alkylamines, such as mono-, di- or tri-lower alkylamines, e.g. ethylamine, tert-butylamine, diethylamine, diisopropylamine, trimethylamine or triethylamine, alkylenediamines, such as lower alkylenediamines, e.g. ethylenediamine, alkylamines substituted by phenyl, such as mono- or di-phenyl-lower alkylamines, e.g. benzylamine or 1- or 2-phenylethylamine, hydroxy-alkylamines, such as mono-, di- or tri-hydroxy-lower alkylamines, e.g. mono-, di- or tri-ethanolamine or diisopropanolamine, oligohydroxy-lower alkylamines, e.g. tris-(hydroxymethyl)-methylamine, hydroxy-lower alkyl-di-lower alkylamines, e.g. N,N-dimethylamino- or N,N-diethylamino-ethanol, amino sugars, such as those in which the amino group is optionally substituted by at least one lower alkyl group, e.g. D-glucosamine, D-galactosamine or marmosamine (derived from monosaccharides in which an alcoholic hydroxy group is replaced by an amino group) or N-methyl-D-glucosamine (an N-lower alkylated amino sugar), cycloalkylamines, such as mono- or di-cycloalkylamines, e.g. cyclohexylamine or dicyclohexylamine, basic amino acids, e.g. arginine, histidine, lysine or ornithine, or cyclic amines, such as lower alkyleneamines or lower alkenyleneamines, e.g. azirine, pyrrolidine, 1-ethyl-pyrrolidine, 2-hydroxyethyl-pyrrolidine, piperidine, 1-ethyl-piperidine, 2-hydroxyethyl-piperidine or pyrroline, or lower alkyleneamines or lower alkenyleneamines in which the carbon chain is interrupted by aza (-NH-), N-lower alkylaza [-N(-lower alkyl)-], oxa (-O-) and/or thia (-S-), e.g. imidazoline, 3-methylimidazoline, piperazine, 4-methyl- or 4-ethylpiperazine, morpholine or thiomorpholine.

Preferred antihistaminic compounds are acrivastine, brompheniramine, chlorpheniramine, dexchlorpheniramine, dimethindene, triprolidine; bromodiphenhydramine, clemastine, phenyltoloxamine, piprinhydrinate, pyrilamine, tripelennamine, cetirizine, hydroxyzine; methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, loratadine, astemizole, diphenhydramine, levocabastine and terfenadine, or pharmaceutically acceptable salts thereof.

Particularly preferred antihistaminic compounds are dimethindene and clemastine, or a pharmaceutically acceptable salt thereof, e.g. dimethindene maleate or clemastine hydrogen fumarate.

A terpenoid compound is, for example, a monoterpenoid compound, a diterpenoid compound, a triterpenoid compound or a sesquiterpenoid compound.

A monoterpenoid compound is e.g. camphor, 3-carene, carvacrol, carvone, chrysanthemic acid; cineol, e.g. 1,8-cineol; gefarnate, geraniol, linalool, limonene, menthol, pulegone or thymol.

A diterpenoid compound is e.g. aphidicolin, forskolin, phytanic acid or phytol.

A triterpenoid compound is, for example, glycyrrhetinic acid or a sapogenin, e.g. oleanolic acid or diosgenin.

A sesquiterpenoid compound is e.g. farnesol or santonin.

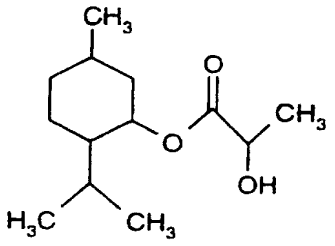
The term "terpenoid compound" is intended also to cover any derivative and any pharmaceutically acceptable salt of a terpenoid compound. Preferred derivatives of a terpenoid compound having one or more hydroxy groups are those wherein one or more of the hydroxy groups are esterified by a carboxylic acid (= terpenoid compound esters).

A carboxylic acid is, for example, a C_1-C_7-aliphatic, a cycloaliphatic, an aromatic, an aromatic-C_1-C_7-aliphatic, a heteroaromatic or a heteroaromatic-C_1-C_7-aliphatic carboxylic acid, which carboxylic acid may be unsubstituted or substituted, for example by one or more substituents selected from hydroxy, halogen, C_1-C_7-alkoxy, carboxy, C_1-C_7-alkoxycarbonyl, cyano, amino, C_1-C_7-alkylamino, di-C_1-C_7-alkylamino, C_1-C_7-alkanoylamino, nitro, C_1-C_7-alkyl and halogen-C_1-C_7-alkyl (e.g.trifluoromethyl). More especially, a carboxylic acid is a C_1-C_7-alkanoic acid which is unsubstituted or substituted by hydroxy, halogen, carboxy or amino, a C_3-C_7-cycloalkanoic acid; a phenyl-C_1-C_7-alkanoic acid, a benzoic acid or a naphthoic acid in each of which the phenyl ring(s) may be unsubstituted or substituted by one or more substituents selected from C_1-C_7-alkyl, halogen-C_1-C_7-alkyl, hydroxy, halogen, C_1-C_7-alkoxy, carboxy, C_1-C_7-alkoxycarbonyl, cyano, amino, C_1-C_7-alkylamino, di-C_1-C_7-alkylamino, C_1-C_7-

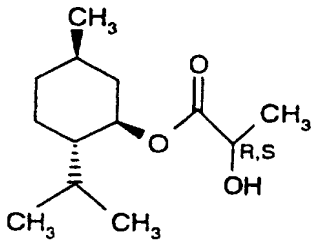
alkanoylamino and nitro; or a heteroaromatic carboxylic acid or a heteroaromatic-C_1-C_7-alkanoic acid in each of which the heteroaromate is selected from furan optionally substituted by C_1-C_7-alkyl or halogen, thiophene optionally substituted by C_1-C_7-alkyl or halogen and pyridine optionally substituted by hydroxy, lower alkoxy, trifluoromethyl, cyano or C_1-C_7-alkyl. In particular, a carboxylic acid is a C_1-C_7-alkanoic acid which is unsubstituted or substituted by hydroxy.

Preferred terpenoid compounds are menthol, menthol esters, especially menthyl lactate, or cineol, more preferably menthol or menthyl lactate, and in one embodiment menthol, and in another embodiment menthyl lactate.

The structural formula of menthyl lactate is as follows:



As the compound contains 4 asymmetric carbon atoms, there are existing 16 different stereoisomers. The term "menthyl lactate" is intended to cover each of these stereoisomers as well as any racemates and any other mixtures of these stereoisomers. Preferred is the racemate of the following structure



which is derived from the naturally occurring (-)-menthol. This compound is available commercially e.g. from Haarmann & Reimer GmbH (Germany) under the name

FRESCOLAT, Type ML. It can also be readily made by processes known in the art by esterifiying the hydroxy group of menthol with lactic acid.

The oral pharmaceutical compositions of the invention have valuable pharmacological properties. Especially they are beneficial in the prevention and treatment of rhinitis, sinusitis, asthma, atopic dermatitis, urticaria and pruritus, and most especially in allergic rhinitis (hay fever), urticaria and pruritus. The beneficial effects of the combinations are especially pronounced, when the terpenoid compound(s) is (are) applied in surprisingly high doses.

The beneficial properties of the combinations of the invention can be demonstrated, for example, in the following tests:

Reduction of wheal induced by histamine injected intradermally in the rat [see Leibowitz et al., Arch. Int. Pharmacodyn. 271 (1984) 135].

Blocking of the histamine-induced bronchoconstriction in anesthetized guinea pigs [see Mauser et al., Eur. J. Pharmacol. 182 (1990) 125-129].

In clinical trials, the beneficial effects of the combinations in e.g. allergen-induced rhino-conjunctivitis are demonstrated. The trial schedule is e.g. as follows: day 1: baseline (challenge with allergen, treatment with placebo); days 2-4: comparative pre-treatment with (a) antihistaminic compound/terpenoid compound (e.g. 1 mg of dimethindene maleate/200 mg of l-menthol thrice a day) or (b) antihistaminic compound alone (e.g. 1 mg of dimethindene maleate thrice a day); day 5 (challenge with allergen). On days 1 and 5, an assessment is made of the clinical symptoms of rhinitis, such as sneezing, rhinorrhoe, nasal itching and conjunctival itching, as well as on nasal flow and resistance (nasal congestion). Treatment with the combination (a) is clearly superior to the treatment with the antihistaminic compound (b) alone.

In another clinical trial, the beneficial effects of the combinations in mild to moderate asthma are demonstrated. In a double-blind, placebo-controlled study the beneficial effects of (a) antihistaminic compound/terpenoid compound (e.g. 1 mg of dimethindene maleate/200 mg of l-menthol twice or thrice a day) and (b) antihistaminic compound alone (e.g. 1 mg of dimethindene maleate twice or thrice a day) are compared. The main assessment criteria

are the asthma score, the use of beta2-agonists (and other medication) necessary and lung function tests, such as FeV_1 (lung volume) and Raw (lung capacity). Treatment with the combination (a) is clearly superior to the treatment with the antihistaminic compound (b) alone.

The oral pharmaceutical compositions obtainable by combining an antihistaminic compound with a terpenoid compound form a further object of the present invention.

Thus the invention further relates to a pharmaceutical composition adapted to oral administration comprising at least one antihistaminic compound and at least one terpenoid compound together with at least one pharmaceutically acceptable carrier.

Preferably, the pharmaceutical compositions according to the invention comprise both the antihistaminic compound(s) and the terpenoid compound(s) in pharmacologically effective amounts.

The dosage of the active ingredients may depend on various factors, such as warm-blooded species, sex, age, weight and individual condition of the warm-blooded animal.

Normally the daily dosage which is administered to a warm-blooded animal weighing approximately 75 kg is of from 0.001 up to 10 mg/kg, especially of from 0.01 up to 7 mg/kg, of the antihistaminic compound and of from 0.1 up to 100 mg/kg, especially of from 0.3 up to 60 mg/kg, more especially of from 0.4 up to 50 mg/kg, most especially of from 1 up to 30 mg/kg and in particular of from 1 up to 15 mg/kg, of the terpenoid compound ("mg/kg" means mg drug per kg body weight of the mammal - including man - to be treated). These doses may be taken once daily or, if desired, also in several, optionally equal, partial doses.

The pharmaceutical compositions of the invention may be in single dose unit form or in non-single dose unit form. If in single dose unit form, they contain e.g. of from 1% up to 90%, preferably of from 10% up to 50%, of the active ingredients (all percentages given are percentages by weight, if not indicated otherwise). Single dose unit forms such as capsules, tablets or dragées contain e.g. of from 10 up to 1000 mg, especially of from 20 up to 800 mg and in particular of from 50 up to 800 mg, of the active ingredients.

In single dose unit forms, the antihistaminic compound(s) is (are) e.g. present in an amount of from 0.05 up to 500 mg, especially of from 0.1 up to 100 mg, more especially of from 0.1 up to 10 mg and most especially of from 0.1 up to 5 mg.

In single dose unit forms, the terpenoid compound(s) is (are) e.g. present in an amount of at least 1 mg, preferably in an amount of at least 10 mg, more preferably in an amount of at least 20 mg, even more preferably in an amount of at least 30 mg, most preferably in an amount of at least 50 mg, in particular in an amount of at least 80 mg, advantageously in an amount of at least 100 mg; more advantageously in an amount of at least 150 mg; and most advantageously in an amount of at least 200 mg; or in an amount of from 1 up to 1000 mg, especially of from 10 up to 800 mg, more especially of from 30 up to 600 mg and first and foremost of from 50 up to 500 mg.

Pharmaceutical compositions for oral administration in single dose unit form are, for example, dragées, tablets or capsules. Moreover, sachets filled with the active substance in powder or granule form come into consideration. All these pharmaceutical compositions are prepared in a manner known per se, for example by means of conventional mixing, granulating or confectioning processes. For example, they can be obtained by combining the active ingredients with solid carriers, optionally granulating a resulting mixture and processing the mixture or granules, after the addition of suitable excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol

and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, e.g. solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate, or polyacrylates, which means homo- or co-polymers of alkyl esters, especially methyl and ethyl esters but also e.g. substituted alkyl esters such as dimethylaminoethyl esters, of acrylic acid and/or methacrylic acid (and also of free acrylic acid and/or methacrylic acid), e.g. Eudragit® products such as Eudragit® S, Eudragit® NE, Eudragit® E or Eudragit® L (e.g. Eudragit® L30-D) of Roehm Pharma GmbH, Darmstadt (Germany). Dyes or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredients.

Other oral pharmaceutical compositions in single dose unit form are e.g. hard gelatin capsules made of gelatin, and soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The hard gelatin capsules may comprise the active ingredients in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules, the active ingredients are preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also be added.

Pharmaceutical compositions in non-single dose unit form are, for example, syrups, liquid suspensions or solutions. They are prepared in customary manner. Typically, they contain the active ingredients in a concentration of from 0.1 up to 50%, preferably of from 0.1 up to 40%, more preferably of from 0.2 up to 30%, most preferably of from 0.5 up to 20%, and especially of from 0.5 up to 10%, or of from 1 up to 20%, or of from 1 up to 10%; or in a concentration that provides a suitable single dose when administered e.g. in a measure of 1, 5 or 10 ml.

In a non-single dose unit form, the antihistaminic compound(s) is (are) typically present in a weight percentage from 0.001% up to 5%, preferably of from 0.005% up to 3%, more preferably of from 0.005 up to 1%, and especially of from 0.01 up to 0.5%.

In a non-single dose unit form, the terpenoid compound(s) is (are) typically present in a weight percentage of at least 0.5%, preferably at least 1%, more preferably at least 2%,

especially in a weight percentage of from 0.1 up to 50%, more especially of from 0.5 up to 30%, most especially of from 1 up to 25%, advantageously of from 1 to 20%, and in particular of from 2 up to 10%.

Pharmaceutical compositions which are in enteric-coated form - and this especially concerns those in single dose unit form - form a preferred embodiment of the invention. Enteric-coated means that the coating is resistant to gastric juice but soluble in the small intestine where the active substances are released.

The following examples are intended to exemplify but not to limit the invention.

Example 1: Soft capsules: 5000 soft gelatin capsules, each comprising 1 mg of dimethindene maleate and 50 mg of menthyl lactate, are prepared as follows.

Composition (for 5 000 capsules)	
dimethindene maleate	5 g
menthyl lactate	250 g
Lauroglycol®	2 l

Preparation process: The dimethindene maleate and menthyl lactate are suspended in Lauroglycol® (= propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground to a particle size of approximately from 1 to 3 µm in a wet pulverizer. 451 mg portions of the mixture are then introduced into soft gelatin capsules by means of a capsule-filling machine.

Example 2: Soft capsules: 5000 soft gelatin capsules, each comprising 1 mg of dimethindene maleate and 50 mg of menthyl lactate are prepared as follows.

Composition (for 5 000 capsules)	
dimethindene maleate	5 g
menthyl lactate	250 g
PEG 400	2 l
Tween 80®	0.01 l

Preparation process: The dimethindene maleate and menthyl lactate are suspended in PEG 400 (= polyethylene glycol with M_r from approximately 380 to approximately 420, Fluka, Switzerland) and Tween 80® (= polyoxyethylene sorbitan monolaurate, Atlas Chem. Ind., Inc., USA, supplied by Fluka, Switzerland) and are ground to a particle size of approximately from 1 to 3 µm in a wet pulverizer. 453 mg portions of the mixture are then introduced into soft gelatin capsules by means of a capsule-filling machine.

Example 3: Dry-fill capsules: 5000 capsules, each comprising 1 mg of dimethindene maleate and 250 mg of menthyl lactate are prepared as follows.

Composition (for 5000 capsules)

dimethindene maleate	5 g
menthyl lactate	1250 g
talcum	100 g
magnesium stearate	20 g
mannitol	280 g

Preparation process: The powdered substances mentioned are pressed through a sieve having a mesh size of 0.6 mm. 331 mg portions of the mixture are introduced into gelatin capsules by means of a capsule-filling machine.

Example 4: Dry-fill capsules: 5000 capsules, each comprising 1 mg of clemastine fumarate and 250 mg of menthyl lactate are prepared as follows.

Composition (for 5000 capsules)

clemastine fumarate	5 g
menthyl lactate	1250 g
talcum	100 g
magnesium stearate	20 g
mannitol	280 g

Preparation process: The powdered substances mentioned are pressed through a sieve having a mesh size of 0.6 mm. 331 mg portions of the mixture are introduced into gelatin capsules by means of a capsule-filling machine.

Example 5: Hard gelatin capsules containing 1 mg of dimethindene maleate and 500 mg menthyl lactate are prepared as follows.

Composition (for 1000 capsules)

dimethindene maleate	1 g
menthyl lactate	500 g
microcrystalline cellulose	200 g
sodium lauryl sulfate	1 g
magnesium stearate	1 g

Preparation process: The dimethindene maleate, menthyl lactate, microcrystalline cellulose and sodium lauryl sulfate are intimately mixed and passed through a dry compactor. Then the magnesium stearate is added and the mass is pressed through a sieve having a mesh size of 1 mm. After stirring for a further 10 min., 703 mg portions of the resulting formulation are introduced into hard gelatin capsules of suitable size.

Example 6: Enteric-coated tablets containing 1 mg of dimethindene maleate and 250 mg of menthyl lactate are prepared as follows.

Composition (for 1000 capsules)

dimethindene maleate	1 g
menthyl lactate	250 g
microcrystalline cellulose	200 g
lactose	70 g
magnesium stearate	1 g
Eudragit® L30-D	20 g
polyethylene glycol	6 g
talc	10 g
distilled water	50 ml

Preparation process: The dimethindene maleate, menthyl lactate, microcrystalline cellulose and lactose are intimately mixed and passed through a dry compactor. Then the magnesium stearate is added and the mass is pressed through a sieve having a mesh size of 1 mm. After stirring for a further 10 min., 522 mg portions of the resulting formulation are pressed to biconvex tablets of 12 mm diameter size. The polyethylene glycol is dissolved in water, then the talc is dispersed in this solution and the Eudragit® L30-D is added upon stirring. This solution is applied to the tablets by the means of a suitable coating equipment.

Example 7: Enteric-coated tablets containing 1 mg of dimethindene maleate and 250 mg of l-menthol are prepared as follows.

Composition (for 1000 capsules)	
dimethindene maleate	1 g
l-menthol	250 g
microcrystalline cellulose	200 g
lactose	70 g
magnesium stearate	1 g
Eudragit® L30-D	20 g
polyethylene glycol	6 g
talc	10 g
distilled water	50 ml

Preparation process: The dimethindene maleate, l-menthol, microcrystalline cellulose and lactose are intimately mixed and passed through a dry compactor. Then the magnesium stearate is added and the mass is pressed through a sieve having a mesh size of 1 mm. After stirring for a further 10 min., 522 mg portions of the resulting formulation are pressed to biconvex tablets of 12 mm diameter size. The polyethylene glycol is dissolved in water, then the talc is dispersed in this solution and the Eudragit® L30-D is added upon stirring. This solution is applied to the tablets by the means of a suitable coating equipment.

Example 8: Solution containing 0.1% of dimethindene maleate and 1% of menthyl lactate is prepared as follows.

10 g of dimethindene maleate are dissolved in 2 l of distilled water, and 100 g of menthyl lactate are dissolved in 2 kg of ethanol. Then these two solutions are mixed with 0.5 kg of glycerin and 5 kg of 70% sorbit solution. The solution obtained is filtered, and the filtrate is filled up to 10 l with distilled water.

Claims

1. Use of an antihistaminic compound in combination with a terpenoid compound for the manufacture of a pharmaceutical composition adapted to oral administration for the prevention or treatment of rhinitis, sinusitis, asthma, atopic dermatitis, urticaria, pruritus or other inflammatory skin conditions.

2. Use according to claim 1, where the antihistaminic compound drug is selected from acrivastine, brompheniramine, chlorpheniramine, dexchlorpheniramine, dimethindene, triprolidine; bromodiphenhydramine, clemastine, phenyltoloxamine, piprinhydrinate, pyrilamine, tripelennamine, cetirizine, hydroxyzine; methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, loratadine, astemizole, diphenhydramine, levocabastine and terfenadine, and pharmaceutically acceptable salts thereof.

3. Use according to claim 1, where the antihistaminic compound drug is selected from dimethindene, clemastine and pharmaceutically applicable salts thereof.

4. Use according to any one of claims 1 to 3, where the terpenoid compound is selected from the group consisting of camphor, 3-carene, carvacrol, carvone, chrysanthemic acid, cineol, gefarnate, geraniol, linalool, limonene, menthol, pulegone, thymol, aphidicolin, forskolin, phytanic acid, phytol, glycyrrhetinic acid, a sapogenin selected from oleanolic acid and diosgenin, farnesol and santonin; wherein any hydroxy group present may be in free form or esterified by a carboxylic acid; and pharmaceutically acceptable salts thereof.

5. Use according to any one of claims 1 to 3, where the terpenoid compound is selected from menthol, menthol esters and cineol.

6. Use according to any one of claims 1 to 3, where the terpenoid compound is selected from menthol and menthyl lactate.

7. Use of an antihistaminic compound in combination with a terpenoid compound according to any one of claims 1 to 6,

where a pharmaceutical composition in single dose unit form is manufactured, in which the antihistaminic compound is present in an amount of from 0.05 up to 500 mg and the terpenoid compound is present in an amount of at least 10 mg, or

where a pharmaceutical composition in non-single dose unit form is manufactured, in which the antihistaminic compound is present in a weight percentage from 0.001% up to 5% and the terpenoid compound is present in a weight percentage of at least 0.5% of the total composition.

8. Use according to any one of claims 1 to 7, where a pharmaceutical composition for the prevention or treatment of rhinitis, sinusitis, asthma, atopic dermatitis, urticaria or pruritus is manufactured.

9. Use according to any one of claims 1 to 7, where a pharmaceutical composition for the prevention or treatment of rhinitis, urticaria or pruritus is manufactured.

10. A pharmaceutical composition adapted to oral administration comprising at least one antihistaminic compound and at least one terpenoid compound together with at least one pharmaceutically acceptable carrier.

11. A pharmaceutical composition according to claim 10,

wherein the terpenoid compound(s) is (are) selected from the group consisting of camphor, 3-carene, carvacrol, carvone, chrysanthemic acid, cineol, gefarnate, geraniol, linalool, limonene, menthol, pulegone, thymol, aphidicolin, forskolin, phytanic acid, phytol, glycyrrhetinic acid, a sapogenin selected from oleanolic acid and diosgenin, farnesol and santonin; in which terpenoid compound any hydroxy group present may be in free form or esterified by a carboxylic acid; and pharmaceutically acceptable salts thereof;

which pharmaceutical composition does not contain a local anaesthetic,

which pharmaceutical composition, if in single dose unit form, contains the antihistaminic compound(s) in an amount of from 0.1 up to 100 mg and the terpenoid compound(s) in an amount of at least 10 mg;

which pharmaceutical composition, if in non-single dose unit form, contains the antihistaminic compound(s) in a weight percentage of from 0.005 up to 3% and the terpenoid compound(s) in a weight percentage of at least 1%;

in which pharmaceutical composition, if in single dose unit form and consisting of one or more cores that are coated, the terpenoid compound(s) is (are) present in the core(s) and may or may not be present in the coating.

12. A pharmaceutical composition according to claim 10 or claim 11, wherein the antihistaminic compound drug(s) is (are) selected from acrivastine, brompheniramine, chlorpheniramine, dexchlorpheniramine, dimethindene, triprolidine; bromodiphenhydramine, clemastine, phenyltoloxamine, piprinhydrinate, pyrilamine, tripelennamine, cetirizine, hydroxyzine; methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, loratadine, astemizole, diphenhydramine, levocabastine and terfenadine, and pharmaceutically acceptable salts thereof.

13. A pharmaceutical composition according to claim 10 or claim 11, wherein the antihistaminic compound drug(s) is (are) selected from dimethindene, clemastine and pharmaceutically applicable salts thereof.

14. A pharmaceutical composition according to any one of claims 10 and 12 to 13, wherein the terpenoid compound(s) is (are) selected from the group consisting of camphor, 3-carene, carvacrol, carvone, chrysanthemic acid, cineol, gefarnate, geraniol, linalool, limonene, menthol, pulegone, thymol, aphidicolin, forskolin, phytanic acid, phytol, glycyrrhetinic acid, a sapogenin selected from oleanolic acid and diosgenin, farnesol and santonin; in which terpenoid compound any hydroxy group present may be in free form or esterified by a carboxylic acid; and pharmaceutically acceptable salts thereof.

15. A pharmaceutical composition according to any one of claims 10 to 13, where the terpenoid compound(s) is (are) selected from menthol, menthol esters or cineol.

16. A pharmaceutical composition according to any one of claims 10 to 13, where the terpenoid compound(s) is (are) selected from menthol or menthyl lactate.

17. A pharmaceutical composition according to any one of claims 10 to 16,

which is in single dose unit form, and in which the antihistaminic compound(s) is (are) present in an amount of from 0.05 up to 500 mg and the terpenoid compound(s) is (are) present in an amount of at least 10 mg, or

which is in non-single dose unit form, and in which the antihistaminic compound(s) is (are) present in a weight percentage from 0.001% up to 5% and the terpenoid compound(s) is (are) present in a weight percentage of at least 0.5% of the total composition.

18. A pharmaceutical composition according to any one of claims 10 to 16, which is in single dose unit form, and in which the antihistaminic compound(s) is (are) present in an amount of from 0.1 up to 100 mg and the terpenoid compound(s) is (are) present in an amount of from 30 up to 800 mg.

19. A pharmaceutical composition according to any one of claims 10 to 18, which is in enteric-coated form.

20. A method of treating rhinitis, sinusitis, asthma, atopic dermatitis, urticaria, pruritus and other inflammatory skin conditions, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of an antihistaminic compound together with a therapeutically effective amount of a terpenoid compound.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/03625

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44 A61K31/40 A61K45/06 //(A61K31/44,31:22), (A61K31/40,31:22)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 9546 Derwent Publications Ltd., London, GB; AN 95-355167 XP002021802 & JP 07 242 536 A (TOYO CAPSULE KK) , 19 September 1995 see abstract ---	1,2, 4-12, 14-18,20
X	WO 95 11671 A (THE PROCTER & GAMBLE COMPANY) 4 May 1995 see page 2-4; claims 1,6,7,9,10; examples 1-6 see example 4 ---	1-6,8, 10-17,20
X A	WO 94 08550 A (THE PROCTER & GAMBLE COMPANY) 28 April 1994 see page 8-11; claims 1,2,4,12,13 --- -/--	1,4-6, 10,14-16 7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 1997	30. 09. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Kanbier, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/03625

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 063 (C-568), 13 February 1989 & JP 63 255219 A (TEIKOKU SEIYAKU KK), 21 October 1988, see abstract & DATABASE WPI Week 8848 Derwent Publications Ltd., London, GB; AN 88-342324 & JP 63 255 219 A (TEIKOKU SEIYAKU KK) , 21 October 1988 see abstract	1,2,4-6, 9,10
X	EP 0 421 825 A (KADEM FARMASEUTIESE PRODUKTIE B.K.) 10 April 1991 see page 2, line 1-36; claims 6,7,14	1,2,4-6, 8-12, 14-16,20
X	WO 94 25009 A (THE PROCTER & GAMBLE COMPANY) 10 November 1994 see page 8; claims 1,4,5,7-13,15; example 2	1-6, 8-16,20
X	CHEMICAL ABSTRACTS, vol. 112, no. 22, 28 May 1990 Columbus, Ohio, US; abstract no. 204754, TAISHO PHARMACEUTICAL CO. LTD.: XP002040990 see abstract & PATENT ABSTRACTS OF JAPAN vol. 014, no. 123 (C-0698), 8 March 1990 & JP 02 000205 A (TAISHO PHARMACEUTICAL CO LTD), 5 January 1990, see abstract	1,2,4-6, 10-12, 14-16,19

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/EP 97/03625

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 20

because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Remark : Although claim 20 is directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 97/03625

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9511671 A	04-05-95	AU 8084594 A	22-05-95
		EP 0725630 A	14-08-96
		JP 9504293 T	28-04-97
WO 9408550 A	28-04-94	AU 5134893 A	09-05-94
		AU 678561 B	05-06-97
		AU 4930793 A	09-05-94
		EP 0662840 A	19-07-95
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EP 421825 A	10-04-91	NONE	
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		CN 1122103 A	08-05-96
		EP 0695175 A	07-02-96
		JP 8509725 T	15-10-96
		NO 954146 A	18-10-95